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Circular Letters:

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Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Aminopteroyl-Glutamic Acid (Aminopterin): Farber, one of the authors, believed that antagonists to folic acid might be of value in the treatment of patients with acute leukemia. This belief was based upon (1) his experience in studies on folic acid deficiency and (2) the occurrence of what he interpreted as an "acceleration phenomenon" in the leukemic process as seen post mortem in the marrow and viscera of children with acute leukemia who had received injections of folic acid conjugates - pteroylglutamic acid (teropterin) and pteroyl diglutamic acid (diopterin).

A series of folic acid antagonists was made available by Dr. Y. Subbarow and his colleagues.

The objective data sufficient to justify research in the direction of antagonists to folic acid in the treatment of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute myelogenous leukemia. Treatment from 17 February to 24 March 1947 with pteroyldiglutamic acid (diopterin) in a dosage of from 100 to 300 mg. intramuscularly daily had no effect upon the hematologic picture. The patient appeared to be moribund. A second bone-marrow biopsy on 25 March verified the diagnosis of myelogenous leukemia. Pteroylaspartic acid, the first antagonist to folic acid to be employed in these studies, was given intramuscularly from 28 March to 4 April in amounts of 40 mg. daily without altering the clinical course. Postmortem examination on 4 April revealed a markedly hypoplastic bone marrow, with a few immature cells. A change of this magnitude in such a short time had not been encountered previously in the marrow of leukemic children.

This observation was followed by clinical, laboratory, and postmortem studies on a group of 14 children with acute leukemia treated with pteroylaspartic acid and on 7 treated with methylpteroic acid. The details of these observations will be reported separately.

Sufficient encouragement was obtained from these observations to justify further studies on the effect of more powerful antagonists to folic acid on the course of acute leukemia in children. Since November, 1947, when a sufficiently pure substance became available, to 15 April 1948, the authors had made studies on 16 children with acute leukemia to whom the most powerful antagonist to folic acid (as determined by growth studies using Streptococcus fecalis R) that they have yet encountered, 4-aminopteroylglutamic acid (aminopterin), was administered by intramuscular injection. Many of these children were moribund at the onset of therapy. Of 16 infants and children with acute leukemia treated with aminopterin 10 showed clinical, hematologic, and pathological evidences of improvement of important nature of three months' duration at the time of this report. Six patients did not respond well; 4 of these are now dead, and 2 were unimproved. This paper presents detailed clinical, hematologic and bone-marrow studies in 5 children selected from these 10 who showed evidences of important improvement; the

course in the other cases was essentially similar. The patients have been selected for the purpose of illustrating some of the problems concerned with the use of aminopterin and because they demonstrate the best results that the authors have observed. The toxic effects are stressed in these histories, and the temporary nature of the remissions is emphasized.

Case 1. W. G., a 7 2/12-year-old boy, entered the hospital for the first time on April 9, 1947, with complaints of joint pain and fever. He had been generally well until 7 weeks before admission, when pain developed in the right knee. There were no associated physical abnormalities, and the pain promptly subsided. Five days later pain recurred in the right elbow, and a low-grade fever was noted. Migratory arthralgia and fever continued until admission.

Physical examination revealed only moderate pallor and slight enlargement of the liver and spleen. The boy appeared well developed and nourished and not particularly ill.

Examination of the blood disclosed a red-cell count of 3,670,000, with a hemoglobin of 10.6 Gm., and a white-cell count of 56,000, with 73 percent blast forms. The platelet count was normal. A bone-marrow biopsy revealed leukemia.

The patient was treated with pteroylaspartic acid beginning on April 16 in doses of from 20 to 60 mg. daily while in the hospital, in a convalescent home, where he remained until May 20, and at home, where the injections were given by the family physician. During that time he was active and fairly well, although the white-cell count remained high and the red-cell count and hemoglobin fell slowly.

On July 1 diopterin, in a dosage of 200 mg. by mouth daily, was begun. This therapy was continued for about 1 month, during which the patient steadily became more ill. The liver and spleen enlarged, and he became very anemic. The blast forms in the peripheral blood rose to 94 percent. Joint pain and fever recurred, and by August 13 he was critically ill, with a temperature reaching 106° F. He was readmitted to the hospital and received several transfusions. Pteroylaspartic acid and methylpteroic acid, in doses of 40 mg. each, were given intramuscularly daily. The patient was discharged after about 2 weeks, and pteroylaspartic acid and methylpteroic acid, in doses of 20 mg. each, were continued in the Tumor Therapy Office. A period of remission ensued, during which the red-cell count and platelets returned to normal levels, the liver and spleen receded in size and the nutrition improved remarkably. He returned to school part time in October and was in quite good condition. The white-cell count had risen to high levels, however, and in November general deterioration began. The liver and spleen enlarged, and he became so anemic that transfusion was necessary by November 24. Only temporary benefit resulted and transfusions were required at about 3-week intervals.

Aminopterin was started on December 16 and given daily, in doses of 0.5 mg. intramuscularly, for six doses. By December 30 the white-cell count had fallen from 60,000 to 19,000. There was moderate improvement in activity and appetite. Thereafter unfavorable weather made daily visits to the clinic impossible, and 1 mg. of aminopterin was given approximately three times weekly for about a month. During that time there was no striking clinical or hematologic improvement, although the patient was not seriously ill.

Daily injections of 1 mg. of aminopterin were begun on February 3 when a bone-marrow biopsy and aspiration revealed 85 percent blast forms, no megakaryocytes and no erythropoiesis. After 10 days, the white-cell count had fallen from 78,000 to 5000, but severe stomatitis made cessation of therapy imperative. Within a week without therapy, the stomatitis had healed completely, and the patient had developed a ravenous appetite. The nutrition gradually improved. By February 21 the liver was no longer palpable, and only the tip of the spleen could be felt. Bone-marrow aspiration and biopsy revealed a slight decrease in blast forms and slight erythropoietic activity. The platelets reached normal levels about 1 month after this course of daily therapy. On March 1 the white-cell count began to rise in spite of daily administration of 0.25 mg. of aminopterin, and by March 6 was 75,000. The spleen again enlarged. The dosage of aminopterin was raised to 1 mg. on March 8, and after about 10 days the white-cell count had fallen to 12,000. Slight stomatitis again appeared, and the dosage of aminopterin was reduced to 0.5 mg. daily, with 1 unit of crude liver extract weekly. The white-cell count has remained at a high-normal level, and the spleen is again slowly receding. The stomatitis is still present but is not progressing and does not interfere with ability to eat.

Case 2. R. P., a 6 4/12-year-old boy, was admitted to the hospital on March 4, 1948, with the chief complaint of increasing pallor. His growth, development and general health had been excellent until about 3 weeks before admission, when tonsillitis had developed. This had subsided promptly, but the patient had become lethargic, and increasing pallor was noted. About 10 days before admission his parents began to notice that he bruised easily.

Physical examination disclosed a well developed and fairly well nourished boy who was very pale and lethargic. Many small ecchymoses were noted over the extremities. The liver edge extended 4 cm. below the costal margin, and the tip of the spleen could be felt at the costal margin. There was slight generalized lymphadenopathy.

Examination of the blood revealed a red-cell count of 1,880,000, with a hemoglobin of 5.65 Gm. and platelets of 46,000, and a white-cell count of 4200, with 20 percent immature or blast forms. A sternal-marrow aspiration revealed 75 percent blast forms. No megakaryocytes were seen.

Shortly after admission the patient developed a spiking temperature up to 104 or 105° F. daily, and rapidly became more lethargic. Blood cultures revealed no growth. Frequent transfusions raised the red-cell count and hemoglobin to normal levels, but there was no favorable clinical response. The white-cell count fell to 1500. He appeared critically ill. On the 7th hospital day penicillin was started, and the temperature decreased although it continued to reach from 101 to 102° F. daily.

On the 8th hospital day, aminopterin (1 mg.) and crude liver extract (1 unit) were given intramuscularly. The white-cell count was 1500. This medication was continued daily, and the patient rapidly became more alert and active. The white-cell count remained near 2000. He was discharged moderately improved on March 15. After discharge he was seen 6 times weekly in the Tumor Therapy Clinic and 1 mg. of aminopterin and 1 unit of crude liver extract were given at each visit. Rapid improvement in appetite and activity continued. A second sternal-marrow biopsy and aspiration after one week of therapy revealed a 25 percent decrease in blast forms and an increase in more mature leukocytes and megakaryocytes. By March 25 the white-cell count had reached 5000, with 34 percent neutrophils, 63 percent lymphocytes and 2 percent blast forms. His activity and appetite were normal and easy bruising was no longer a complaint. At about that time he developed minor lesions of the oral mucosa. The dosage of aminopterin was reduced to 0.5 mg., and the liver extract was given once weekly. Steady improvement has continued. The liver and spleen are no longer palpable. The patient is active in outdoor games, and his endurance is good. On March 31 he returned to school, where his teacher noted marked improvement in his appearance and interest. Sternal-marrow aspiration on April 1 revealed a slight further reduction in blast forms, a moderate increase in megakaryocytes and a marked increase in erythropoiesis. He continues on daily injections of 0.5 mg. of aminopterin with liver extract once weekly.

Case 3. G.J., a 3 8/12-year-old boy, was admitted to the hospital on November 2, 1947 - 5 days after the onset of an acute illness with sore throat and fever.

The past history, birth, and developmental history were not remarkable.

Physical examination disclosed a critically ill patient with an acute follicular tonsillitis and enlarged tender cervical lymph nodes. There was no generalized adenopathy and no hepatomegaly or splenomegaly. A blood culture was positive for beta-hemolytic streptococcus.

Examination of the peripheral blood showed a red-cell count of 1,900,000, a white-cell count of 480 and a platelet count of 123,000. Bone-marrow aspiration showed 16.4 percent blast forms, 3.2 percent mature polymorphonuclear leukocytes, 76.2 percent lymphocytes and 1.6 percent erythroid elements. On the basis of the bone-marrow aspiration a diagnosis of leukemia was made. The bacteremia was treated with penicillin and streptomycin.

After recovery from the infection the patient went into a complete clinical and hematologic remission for about 2 months. At that time bilateral acute otitis media developed. Two weeks later the total nucleated count of the sternal bone marrow was 910,000 (normal from 200,000 to 250,000), with 96 percent blast forms. By February 26, 1948, the white-cell count was 17,250, with 80 percent blast blast forms, the spleen extended to the umbilicus, petechiae began to appear, and it was obvious that the child was entering a rapidly progressive phase of the leukemia.

He was readmitted to the hospital on March 6. He appeared chronically ill, with pallor, petechiae, moderate generalized lymphadenopathy and marked hepatomegaly and splenomegaly. The white-cell count, which was 30,400, with 86 percent blast forms, on admission, fell rapidly to 900 by March 12, and the patient appeared moribund. Blood cultures were negative.

Aminopterin was started on March 13 in doses of 0.5 mg. and given for 5 consecutive days. Crude liver extract, in a dosage of 1 unit daily, was given in the same syringe. At the end of that time there was no noticeable clinical improvement, but the white-cell count, which was still 900, contained only 5 percent blast forms. A sternal-marrow smear made at the end of this short period of therapy and compared to one just before therapy was started showed a shift to the right, with some reduction in blast forms and an increase in more mature forms of granulocytes, as well as a slight increase in erythroid elements. Aminopterin was discontinued until it became apparent that the leukopenia was not increasing.

After 4 days without treatment 0.5 mg. of aminopterin daily, with 1 unit of crude liver extract, was given once more. The white-cell count increased gradually, and blast forms disappeared from the peripheral blood. The child began to show clinical improvement, his appetite became better, and the liver and spleen became scarcely palpable. The petechiae and generalized adenopathy disappeared.

At the present writing there is a partial contracture of the left leg, probably resulting from leukemic infiltrations about the knee joint and in the gastrocnemius muscle. The tip of the spleen is still palpable. Otherwise the child is normal on physical examination. The white-cell count is 6700, with a normal differential. The platelet count is 152,000. Aspiration of the sternal marrow on March 29

revealed 8 percent blast forms, with an increase in more mature granulocytes, erythrocyte precursors and megakaryocytes.

Case 4. C.C., a 2 1/12-year-old girl, was admitted to the hospital on August 22, 1947. Six weeks previously her father had noticed lumps about the head and neck. Two weeks previously her family physician had made a diagnosis of leukemia on the basis of a peripheral blood smear.

Physical examination revealed a pale girl, with ecchymotic areas over the lower extremities. There was marked generalized adenopathy, particularly about the parotid region, and the liver edge and tip of the spleen extended down to the iliac crests.

Examination of the blood disclosed a white-cell count of 75,000, with 80 percent blast forms. The platelet count was 54,000. The patient was discharged and given x-ray therapy to the parotid region in the outpatient department. A total of 600 r was given from September 4 to September 8. The white-cell count, which was 94,000 on September 4, had dropped to 5000 by September 11.

The patient was readmitted on September 27. She was much worse, with a poor appetite, marked pallor and massive adenopathy. The white-cell count was 1000, with 30 percent blast forms. Several transfusions before discharge produced only slight improvement.

The third admission, on November 6, followed a generalized convulsion. The patient was comatose, with a temperature of 103.6° F.

Physical examination was essentially unchanged except that the kidneys were definitely enlarged and easily palpable. There was no positive evidence of infection. A transfusion and penicillin were given, and the patient was discharged in fair condition.

The fourth and last admission was on December 2, when there was a temperature of 105° F. There was a severe stomatitis and pharyngitis, with extensive exudation. The left ear was inflamed but not suppurating. Bronchopneumonia was present on the left. A lumbar puncture showed evidence of subarachnoid hemorrhage. A blood culture was positive for Staphylococcus aureus, coagulase positive.

For the first 6 hospital days the patient ran a septic temperature ranging between 105 and 103° F. She was given penicillin and sulfadiazine, as well as repeated blood transfusions, throughout the hospital stay. At this admission she was seen for the first time by the Tumor Clinic and received 20 mg. of teropterin per day for eighteen doses, from December 3 through December 20.

On several occasions the patient appeared moribund but on about the 7th hospital day she began to improve and continued to improve until the time of her discharge. The white-cell count, which had dropped to 650 on the 4th hospital day, rose to 6400 on the day before discharge. The differential count included 68 percent neutrophils, 24 percent lymphocytes and 8 percent monocytes. There were no blast forms.

After this severe infection there was a remission in the clinical and hematologic condition. During that time the patient was given an occasional dose of teropterin to a total of 140 mg. By January 13 small lymph nodes over the scalp, parotid and cervical regions had begun to develop. These rapidly increased, and by January 19 there was massive generalized adenopathy. The peripheral blood and bone marrow continued at values approaching normal. There were only occasional to 5 percent blast forms in the peripheral blood, with a normal total white-cell count, and 8.4 percent blast forms in the bone marrow, with a slight depression of mature forms and a moderate depression of erythroid forms. On January 20 aminopterin was started in doses of 1 mg. daily with 20 mg. of teropterin daily. This was given on twenty-six clinic visits from January 20 to February 21. Four days after treatment had been started there was a marked decrease in the size of all the lymph nodes. In 2 weeks the patient was normal on physical examination. Her appetite became very good, her disposition happy, and she began to play and run about like a normal child. Her parents stated that her condition was better than she had been before she became sick for the first time. Since treatment was stopped she has continued to do well. She has been without treatment since February 21 and at present is completely normal on physical examination. The total white-cell count is 9000, with an occasional blast form. The platelet count is 256,000, the red-cell count 4,600,000, and the hemoglobin 14.8 Gm.

Case 5. R.S., 2 2/12-year-old boy, was admitted to the hospital on August 26, 1947, with the chief complaint of increasing pallor. He was one of identical twins, and his birth, growth and development, and general health had been unremarkable. About 10 days before admission he had developed a low-grade fever, soon followed by increasing pallor, lethargy, anorexia and intermittent vomiting.

Physical examination showed a fairly well developed and well nourished and only moderately ill boy. He was very pale. There was generalized enlargement of the lymph nodes and moderate hepatomegaly and splenomegaly. X-ray study showed marked infiltration of the long bones. The hemoglobin was 5.5 Gm., and the white-cell count 12,400, with 41 percent immature or blast forms.

During 2 weeks in the hospital the patient received transfusions, which restored the hemoglobin to normal levels. After discharge he was seen in the Tumor Therapy Clinic daily except Sunday and on each visit received 20 mg. of pteroylaspartic acid intramuscularly. He continued on this regimen for about 2 months, during which the disease progressed slowly but steadily. He became less alert and less active. He developed a limp. There was gradual weight loss, and the liver and spleen continued

to enlarge. The leukocytes remained at normal levels but the percentage of blast forms increased. The red-cell count and hemoglobin slowly fell, until on November 6 it was necessary to admit him to the hospital for transfusion. At that time a small pathologic fracture was noted in the left tibia. After discharge he was seen in the Tumor Therapy Office three times weekly and on each visit received 40 mg. of pteroylaspartic acid intramuscularly. Late in November there was a definite acceleration in the progress of the disease. The white-cell count began to rise, and the platelets fell. The patient began to bruise easily and had occasional slight oozing from the gums. He developed moderate exophthalmos. He refused to walk. Hospitalization was necessary twice in the early weeks of December for treatment of arthritis and upper respiratory infection. Sternal-marrow aspiration at that time revealed 40 percent blast forms and little erythropoiesis. By the end of December the patient appeared moribund. He had marked generalized adenopathy, marked hepatomegaly and a spleen whose tip extended into the pelvis. There was moderate dyspnea and stridor, pallor, marked wasting and exophthalmos. There were many ecchymoses, and oozing occurred at the gingival margins.

Aminopterin therapy was begun on December 28. On each of 3 successive days the patient received 1.0 mg. of the drug intramuscularly. During that time the white-cell count began to fall rapidly from the pretreatment level of 60,000. By December 31 the count was 9000, and respiratory difficulty was even more marked. He was admitted to the hospital, aminopterin was discontinued, and a transfusion was given. He was discharged on January 3, 1948, slightly improved, but with the white-cell count only 2700. After discharge he was again followed in the Tumor Therapy Clinic. By January 13 marked clinical improvement had become apparent. The patient was walking for the first time in 2 months, and respiratory difficulty had disappeared. His appetite was ravenous. There was no more bleeding. "His clothes became loose about the abdomen." On January 27 the white-cell count reached 5000, and 0.5 mg. of aminopterin was started and given three times weekly. Gradual improvement continued, but a white-cell count of about 3000 persisted. In the middle of February, teropterin in 10-mg. amounts was given with each dose of aminopterin for five doses. Early in March a rise in the hemoglobin and red-cell count began. Since then folic acid for a time and lately crude liver extract have been used in conjunction with aminopterin. There had been steady clinical and hematologic improvement so that at the time of writing, activity, alertness and nutrition are equal to or better than those of the well twin. The liver and spleen have decreased in size, so that they are barely palpable beneath the costal margins. Exophthalmos has disappeared. The red-cell and white-cell count, differential counts and platelets are within normal limits. The sternal marrow, examined by biopsy, is normally cellular, and the differential count is normal. Erythropoiesis is active, and megakaryocytes are present in normal number.

The observations on these patients show that the aminopterin has a marked effect upon the leukemic bone marrow and upon the immature cells in the peripheral blood, and judging from the disappearance of enlargement of the spleen, liver, and lymph nodes (when those organs were enlarged), very probably on leukemic deposits in the viscera as well.

This report describes only temporary remissions produced by the injection of aminopterin in children with acute leukemia. It is impossible to state whether the substance will be of value for a longer period than that covered by these studies. The toxic effects may make continued use of the drug impossible. One patient (Case 4) had been without treatment for 43 days after having had a satisfactory remission. During this time the peripheral blood and the sternal bone marrow became essentially normal. At the end of 47 days without treatment a few nodules appeared beneath the scalp and in the subcutaneous tissue over the face. It is probable that these represent leukemic deposits, although at the time of their appearance the peripheral blood was still essentially normal. Because of this finding the treatment has been reinstituted. After ten days of treatment with aminopterin, the nodules have disappeared once more.

These studies justify a search for other antagonists to folic acid that are less toxic than aminopterin and may be even more powerful. (New England J. Med., 3 June '48 - S. Farber et al.)

A Comparison of the Toxic Manifestations Produced by Benadryl and Pyribenzamine: Both experimentally and clinically pyribenzamine and benadryl have been demonstrated to possess qualities powerfully antagonistic to histamine. Upon this common feature much of their efficacy in the treatment of allergic disease appears to rest. In addition to this, benadryl shows a minor but still powerful hyoscine-like action not fully shared by pyribenzamine. This provides, in addition to the antihistaminic effect, a mild sedative action.

Although there is rather general agreement regarding the nature of the side effects following the use of both benadryl and pyribenzamine, there is marked difference of opinion concerning their incidence and severity. To date, all or nearly all of the observations regarding these points have been recorded in the course of treatment of allergic diseases and are therefore subject secondarily to all the influences surrounding the allergic episode. Moreover, there has been no concerted effort to compare the reactions of both drugs in the same subject. Thus, the personal equation of the subject has never been eliminated from the final evaluation of the results. In an effort to accomplish these objectives and to afford a sound basis for the comparison of the toxic activity of these antihistaminic compounds over the entire range of therapeutic dosage, the present study was undertaken.

Ambulatory patients from a general medical clinic of a city hospital were chosen at random except that those with acute illnesses, allergic complaints, or recognizable disturbances of the autonomic nervous system were excluded. The underlying conditions for which these patients sought relief included arthritis, hypertension, arteriosclerosis, and minor upper respiratory, muscular, or digestive complaints. Each subject was further tested for his or her fitness to participate in the investigation by the use of a placebo which resembled the corresponding antihistaminic compound in all its physical characteristics.

In all, 142 subjects, 80 women, and 62 men ranging in age from 18 to 80 with an average of 44.7 years, completed the tests. Of these, 52 were studied while taking benadryl only, 52 while receiving pyribenzamine only, and 38 while ingesting successively each of the two antihistaminic compounds. In the last-mentioned subjects a period of 14 days or more elapsed after one drug had been used before the second was started. Each drug was tried for not less than one week, and any given level of dosage was continued in each subject for not less than one week. A number of subjects were given gradually increasing doses of one or the other drug. The patient continued at each level of dosage for at least one week. Therefore, some patients received one or the other of the antihistaminic compounds for periods lasting from 4 to 8 weeks. However, gradually increasing doses of the drug were avoided in the majority of instances because there was thus produced a tendency to build a tolerance against the unpleasant reactions to the compound.

In order to establish a relatively long-term comparison between the two drugs, each of 6 subjects was successively followed on gradually increasing

doses of first one drug and then the other at daily levels of 150, 300, 450, and 600 mg. respectively. In these subjects each increment in the amount of compound ingested was made after a period of not less than 7 days at the immediately preceding level of dosage. Two weeks or more elapsed following the use of one preparation before the other was started. All observations were checked by the same technics and personnel.

All side effects were recorded, regardless of their severity. When lower levels of dosage (from 150 to 300 mg.) were used, side effects rarely precluded the continued use of the drug. However, their frequency warrants a continued search for more nearly ideal agents.

It is clear from the results of this study that the intensity and number of cerebral manifestations is greater with benadryl than with pyribenzamine. It is equally evident that symptoms referable to the gastro-intestinal tract are much more frequent with pyribenzamine than with benadryl. When the over-all incidence of all reactions is assessed, there is little difference between the two drugs at lower levels of dosage, that is from 150 to 300 mg. daily. Indeed, the greater drowsiness caused by benadryl is often of therapeutic importance, particularly in the itching dermatoses and in asthma. However, when higher levels of dosage (from 450 to 600 mg.) are employed, benadryl is decidedly the more toxic of the two drugs and may cause confusional states not unlike those seen following alcoholic excesses.

It seems that far too much emphasis has been placed upon the relatively high incidence of reactions to benadryl, for instance, 75 percent, as compared with the infrequency of reactions to pyribenzamine, for instance, 25 percent or less. Indeed, in the usual range of therapeutic dosage (from 150 to 300 mg. daily) a critical evaluation shows that this wide difference does not exist. Moreover, many of the unpleasant symptoms produced by benadryl in such amounts are actually accounted for by its sedative action, which, as stated above, may sometimes be gainfully employed. At higher levels of dosage benadryl becomes definitely the more toxic of the two antihistaminic substances and should be used at such levels only when the patient can be under more or less constant surveillance. The gastro-intestinal irritation resulting from the use of pyribenzamine at similarly high levels of dosage usually precludes its use in the majority of patients.

A direct relationship between the degree of therapeutic effectiveness and toxicity does not seem to exist. It appears likely, therefore, that the antihistaminic factor is not responsible for the untoward symptoms, but that some other property of each of these drugs plays a dominant role in producing side effects. This apparent dissociation between antihistaminic and toxic properties of these drugs furnishes a real incentive to continue the search for agents which will possess the antihistaminic factor to the complete or nearly complete exclusion of the toxic factor. (J. Lab. and Clin. Med., May '48 - T. H. McGavack et al.)

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Penicillin in the Treatment of Actinomycosis: Although penicillin has been used by various investigators since 1943 in the treatment of actinomycosis, no definite conclusions have been drawn concerning its efficacy in this disease. In the first instances in which it was used the penicillin seemed to be ineffective, probably because of inadequate dosage. In subsequent cases the observations were limited.

The present report deals with the authors' observations on the use of penicillin in the treatment of 46 patients who had actinomycosis. These 46 patients have been followed for periods of from 1 to 5 years since the conclusions of the treatment.

Considerable confusion and difference of opinion exist concerning the definition of the term "actinomycosis." For the purposes of this investigative work the authors have confined their studies to infections caused by the microaerophilic organism, Actinomyces bovis. Infections caused by the several species of the genus Nocardia have been classified separately and are not included in this report. The diagnosis of actinomycosis in each of these patients was made by direct examination or culture of pus obtained from a draining sinus or from material obtained at operation. All strains of Actinomyces bovis cultured were found to be sensitive to penicillin in vitro, the organism being inhibited by from 0.01 to 0.1 unit of penicillin per cubic centimeter of culture medium.

In attempting to evaluate methods of treatment it is of importance to qualify carefully the general term actinomycosis, for the prognosis varies greatly according to the location of the lesion, the duration of the infection, and the general condition of the patient. A method of treatment which is effective when the soft tissues of the face and neck are involved is often entirely ineffective when actinomycosis involves other parts of the body. If the disease has been present sufficiently long to permit an overgrowth of fibrous tissue or an impairment of the general health of the patient, effective treatment of any type will be much more difficult. A classification of actinomycosis according to the organ or organs involved is the most desirable. However, inasmuch as the pathologic process and the prognosis are similar when certain regions of the body are invaded, for purposes of discussion a more general classification can be adopted. These patients, therefore, have been grouped under five general headings: cervicofacial actinomycosis, pulmonary actinomycosis, abdominal actinomycosis, pelvic actinomycosis, and actinomycosis involving other parts of the body.

Of this series of 46 patients, 26 were suffering from cervicofacial actinomycosis, 9 from pulmonary actinomycosis, 8 from abdominal actinomycosis, and 3 from pelvic actinomycosis. Penicillin was administered to each of these patients either by intermittent intramuscular injections every 3 hours or by the continuous intravenous drip method. The dosages of penicillin varied widely between 80,000 and 1,000,000 units daily. In most cases penicillin was administered continuously for periods ranging from 2 to 7 weeks. In some instances the penicillin was administered in courses of 10 days each, with periods of from one to several weeks intervening.

The results from this study appear to indicate that penicillin is an effective agent in the treatment of actinomycosis, its effectiveness varying somewhat with the location of the lesion. As is true in most infections, actinomycosis varies greatly in different individuals. Apparently in some cases of mild actinomycosis, complete recovery from the infection occurs without treatment. How often spontaneous recovery occurs is difficult to determine, for it is not until the disease has become quite extensive that a clinical and bacteriologic diagnosis can be made. However, when the infection has become well established, spontaneous cures occur only rarely.

Cervicofacial actinomycosis has responded well to several methods of treatment. Prolonged surgical drainage, roentgen therapy, and administration of the iodides and some of the sulfonamide compounds have proved of value in the treatment of actinomycosis when it involves the neck or face. However, penicillin appears to have definitely shortened the duration of the infection and the period of treatment. Of the 26 patients suffering from cervicofacial actinomycosis, 24 had excellent results which were obtained after an average period of treatment of less than 2 months, a period significantly less than the usual length of time required to obtain comparable results when penicillin was not used. In cases of cervicofacial actinomycosis of short duration, the use of penicillin alone has resulted in cures. When the infection has been extensive and of long duration, use of penicillin has been combined with surgical treatment. In most of the cases in which penicillin has been used, the sinuses closed rapidly and the patients recovered completely in a relatively short time. Even the two patients who did not recover completely improved markedly while under treatment. Drainage from the sinuses ceased entirely, and the infection appeared to be cured at the time treatment was discontinued. However, in these two patients evidence of active infection appeared again several months later.

In some cases of cervicofacial actinomycosis death occurs from extension of the infection into the meninges. One of these patients was critically ill, with evidence of meningitis secondary to cervicofacial actinomycosis. Penicillin was administered for 6 weeks and the patient recovered.

Pulmonary actinomycosis nearly always has been a progressive and fatal disease. The prognosis has been particularly unfavorable when the parenchyma of the lung has been invaded. The usual methods of treatment have been ineffective in most cases. The recovery, after treatment with penicillin, of 5 of the 9 patients who had pulmonary actinomycosis is, therefore, most encouraging. Moreover, two of the patients for whom the results were listed as failures are in good general condition, although they still have evidence of active disease.

Abdominal actinomycosis has always been a serious disease, but good results have been obtained in occasional patients by several different methods of treatment. However, the percentage of patients who recovered has never been very great and the prognosis, therefore, has been poor. Of the 8 patients with abdominal actinomycosis who received penicillin, 6 recovered. It appears,

therefore, that penicillin is a very effective chemotherapeutic agent in the treatment of abdominal actinomycosis.

Actinomycosis involving the pelvic viscera in women may well be merely a localized form of abdominal actinomycosis. However, the prognosis when actinomycosis involves the pelvic organs has been extremely poor, and very few recoveries ever have been reported. The recovery, therefore, after treatment with penicillin, of the three women who had actinomycosis involving the pelvic viscera seems particularly significant.

In the treatment of all types of actinomycosis, a dosage of at least 500,000 units of penicillin daily administered intramuscularly or intravenously for a period of six weeks appears to achieve the best results. Adequate drainage is indicated if abscesses are present.

Because the authors have been attempting to evaluate the effectiveness of penicillin in the treatment of actinomycosis, other forms of therapy, aside from surgical drainage or excision of diseased tissue, have been avoided so far as possible in the treatment of these patients. It seems possible, therefore, that even better results can be achieved in the future if administration of adequate amounts of penicillin is combined with the use of sulfonamide compounds or of streptomycin. (J. Lab. and Clin. Med., May '48 - D. R. Nichols and W. E. Herrell)

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The Healing of Bowel as Influenced by Sulfasuxidine and Streptomycin: The value of sulfasuxidine and sulfathalidine since their introduction as intestinal antiseptics in 1941 and 1943 respectively has been repeatedly and amply demonstrated in both the clinical and experimental use of these bacteriostatic agents. More recently oral streptomycin has been suggested for a similar purpose.

It has been demonstrated previously that these sulfonamides favor the healing of the colon in dogs following anastomosis. With the introduction of streptomycin as an intestinal antiseptic to effect an alteration of the bacterial flora, its influence upon bowel healing is likewise being studied. Two types of anastomosis were investigated: (1) an open technic using a single continuous row of chromic catgut placed through the entire thickness of the wall of the colon; and (2) a so-called aseptic procedure using two rows of sutures which included the submucosa but which did not penetrate the mucosa.

End-to-end anastomoses of the descending colon were performed in 16 control dogs, in 16 dogs which had received sulfasuxidine therapy preoperatively and postoperatively, as well as in 12 dogs which received both sulfasuxidine and streptomycin. An open technic of anastomosis was used in 18 treated and 12 control animals, and a closed technic was utilized in 10 treated and 4 control animals. The

surviving animals were sacrificed on the 3rd, 5th, and 7th postoperative days, and gross and microscopic studies were done to determine the state of healing. In the control dogs there was a high percentage of wound infection and peritonitis with 3 perforations and 3 deaths. Sections of bowel in all the control dogs showed a marked inflammatory reaction and retarded healing. All of the treated animals survived, and there were no instances of wound infection, peritonitis, or perforation. Sections of the bowel in all of the treated animals showed minimal inflammatory reaction and rapid, well-organized healing resembling that of a clean wound. When the closed technic was used in the control dogs, the results were somewhat better than when the open technic was employed. However, in the treated animals the results were uniformly good whether the open or closed technic was used.

These results present additional evidence of the value of sulfasuxidine in the preoperative preparation and postoperative care in surgical procedures on the bowel, and demonstrate that open technics of anastomosis may be more safely utilized when sulfasuxidine has been adequately administered.

Streptomycin administered orally failed to maintain an alteration of the bacterial flora for a sufficient length of time to permit its experimental evaluation in healing of the large bowel. When it was given simultaneously with sulfasuxidine, the results were essentially those observed when sulfasuxidine was given alone.

The operation of bowel suture always results in contamination of the tissues which are being approximated. It is possible to avoid visible soiling, but bacterial contamination of the innermost edges of the apposed bowel wall occurs during the first few minutes after the inner row of sutures is applied, even though a closed "aseptic" technic is used. Consequently, healing of the colon following anastomosis must simulate that of a contaminated wound. This fact is quite conclusively demonstrated in the microscopic sections taken across the suture line. The lessened extent to which this occurs when the bacterial flora has been simplified and attenuated by intestinal antiseptics must account for the improvement and rapidity of healing observed following the administration of sulfasuxidine.

The difference of healing between the control and treated animals was so striking as to resemble secondary repair in the first instance and primary healing following the alteration of the bacterial flora.

The mechanical aspects of fecal material remaining in the bowel at the time of operation are important. In these experiments, the long period of low residue diet, magnesium sulfate given the control animals 12 hours before operation, and a large dose of morphine one hour preceding anesthesia completely emptied the colon of the control animals. The treated animals received no purgation and a small quantity of liquid fecal material was present. No attempt was made to avoid gross soiling during open anastomosis in the treated

animals. There were no abdominal wound infections in this group, a fact which is contrary to the usual infection observed in the wound following open anastomosis in the control series. (Surg., Gynec. and Obstet., June '48 - E. J. Poth et al.)

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Reduction of Overweight Without the Use of Hormones: This report is based on the study of a group of obese patients, totaling 50 in number and varying in age from 34 months to 55 years. All had been referred for endocrine treatment either because of debilitating overweight, presumably due to some vague endocrinopathy, or because of some specific endocrine dysfunction with which the overweight was associated. The specific glandular dysfunction which had been tentatively diagnosed in some of these patients in the general medical clinic was definitely established, or ruled out, in the endocrine clinic by special laboratory investigations, special physical examinations, and more detailed history. These specific endocrinopathies were mostly hypofunction of the gonads, and because they did not seem to impair the health or well-being of the patient at the time, they were disregarded. Some of the patients were treated for obesity for the first time. Others had previously attempted to reduce on a carefully calculated low caloric diet and could not adjust to such a regimen. A small number had previously taken hormone products with failure to lose weight. The group was thus heterogenous, consisting of some patients treated for obesity for the first time, and others re-treated after endocrine therapy and carefully calculated low caloric diets had failed. No patient with diabetes or marked hypothyroidism was included in this study. Weight reduction in these patients was handled as any other major medical problem and the patient reported to the physician at each clinic visit.

Before the initiation of treatment for obesity, the patient underwent the physical examination necessary in special endocrine cases, and a careful medical history with special reference to inherent and acquired endocrine disturbance was taken. Laboratory tests made at the beginning, and whenever possible, at the end of the period of weight loss, included basal metabolism, glucose tolerance, urine analysis, complete blood count, and determination of blood cholesterol, blood calcium, and blood phosphorus. Roentgenography of the sella turcica and epiphyses was requested whenever other findings suggested that such study might be helpful or essential.

Hormonal products were definitely not prescribed or used during the entire period of weight reduction. No calculated caloric diet was suggested; consequently there was no need for the services and advice of dieticians. But much emphasis was placed upon the need for re-education of the appetite. These overweight patients were informed that there were no known hormones that could cure the obesity, but that their adiposity could be satisfactorily reduced by strictly adhering to a prescribed dietary. They were warned that if the previously faulty food habits were again indulged in, increase in weight would recur.

A list of food substances chosen to constitute a high protein, low fat, low carbohydrate diet, with no calculation of caloric values was then prescribed. It included lean meat, fish and fowl in large portions, approximately double or more the amount of a normal serving at least twice daily. All possible fat was scrupulously removed from the meat, and no fat as such, either animal or vegetable, was added. Two eggs daily were advised, and also uncreamed cottage cheese and gelatin. The vegetables included cabbage, cauliflower, broccoli, brussels sprouts, kraut, spinach, celery, asparagus, string beans, onions, radishes, lettuce and other greens, cucumbers, mushrooms, summer squash, tomatoes, rhubarb, endive, okra, and eggplant. The fruit consisted of grapefruit (either canned or fresh, but always unsweetened), and strawberries and cranberries sweetened with saccharin. Lemon juice and vinegar were also included. The habits of taking tea, coffee, and salt were discussed and not interfered with unless there was a special contraindication or unless the amounts used had been excessive. If the patients were immoderate salt eaters, they were advised that the amount of salt added to the food in the process of preparing the meal was usually quite adequate. Inasmuch as the patients were allowed to choose what they desired from the above list and to eat ad lib., to insure against certain mineral and vitamin deficiencies, calcium, in the form of calcium lactate (from 30 to 40 grains), vitamin D (from 600 to 1000 U.S.P. units), and from 12 to 15 plain brewer's yeast tablets (7 and 1/2 grains each) were included as a fixed part of their daily dietary intake.

In the first group of obese patients were those, ranging in age from 14 to 50 years, with body configurations of the type commonly described as pituitary obesity, in which the overweight has been presumed to be due to hypofunction of the pituitary. Reduction in body weight in individuals of this group varied from 12 to 102 pounds. The absolute number of pounds lost by each individual depended upon the initial body weight and the length of time that the patient continued this dietary regimen.

In the second group were those obese women most commonly found in clinical and office practice, namely, the post-menopausal women who console themselves with the idea that their continuous gain in weight is due to cessation of ovarian function. Typical of this class is a large apron of fat, pendulous breasts, and the girdle type of obesity. Weight loss in this group varied from 27 and 1/2 to 102 pounds. The usual diagnosis was menopausal obesity.

In the third group there were obese women in the child-bearing years. In addition to obesity a definite diagnosis of hypofunction of the ovaries had been established. No ovarian stimulating substance or other hormones were prescribed during the period of weight reduction. Weight loss up to 117 and 1/4 pounds was recorded. Hypogonadal obesity is the usual clinical diagnosis in this type of case.

In the fourth group of obese patients were those who had undergone major pelvic surgical operations, followed by cessation of menstruation. These

patients likewise had been diagnosed clinically as having hypogonadal obesity, but were differentiated from the preceding group because of extirpation of ovaries at some previous date which resulted in surgical menopause. The same satisfactory loss in weight on this dietary regimen was observed in this group.

In the fifth group were overweight juvenile patients with clinical diagnoses of the Fröhlich-syndrome type of obesity. Seven patients of this type (three males and four females) were studied. They varied in age from 34 months to 18 years. In all, only the high protein, low fat, low carbohydrate ad lib. dietary for weight reduction was used. Weight loss of more than 50 pounds was accomplished on this regimen before specific gonadal therapy was instituted. One outstanding case of hyperadrenocorticism with hypo-genitalism, striae, polycythemia, acne, and hypertension was included in this group.

A few of the patients in this series had given a history of increased appetite with resultant excessive food intake; but most of them had acquired a taste for carbohydrates and indulged in them in excess of the amount which their body could metabolize without excessive deposition of fat. The fundamental cause of their obesity seemed to be due to some unknown constitutional discrepancy in their metabolism. This makes it necessary for them to exist on a diet containing a greater proportion of protein and less carbohydrate and fat than is required for the individual who does not become excessively obese on the average American dietary. Be that as it may, the fact remains that no endocrine product known to therapeutics is necessary or helpful in reducing the body weight of obese patients.

Thyroid hormones should be administered solely for the correction of a specific hypothyroidism. When this is properly accomplished, the obesity will take care of itself, or it should be managed by dietary regulation. The use of thyroid extract, in patients with adiposity but with no hypothyroidism, solely for the purpose of attempting to effect weight loss by stimulating metabolism, is ineffective. Such overweight patients soon manifest the symptoms of severe induced hyperthyroidism with little or no weight loss.

Glucose tolerance determinations on these obese patients indicated that some of them had a reduced glucose utilization, as has been previously reported. Others showed a slightly increased, or normal tolerance. Most patients, initially, with a reduced utilization of glucose manifested a tendency toward a more normal glucose tolerance curve after following this dietary for from 4 to 6 months, during which time there was a reduction in body weight of from 40 to 60 pounds.

Hypertension was present as a complicating factor in a few of these patients before the onset of the weight reduction regimen. The highest systolic pressure was 220 mm. of mercury. Blood pressure levels were checked from time to time to determine the effect of the high protein intake on this mechanism. No instance of either an increase in existing hypertension or an elevation in the

normal blood pressure was observed during this dietary regimen. On the contrary, in some instances in which hypertension initially existed, there followed an appreciable reduction in both systolic and diastolic levels after the body weight had been reduced by from 30 to 60 pounds. Similar results have been observed in obese patients with hypertension following reduction in body weight by other methods.

Endocrine obesity is a term which is misleading in that it conveys to the obese patient a false idea, suggesting that his obesity is due to some specific endocrine glandular deficiency which can be corrected by endocrine therapy. This causes the patient to seek needless endocrine medication, whereas dietary measures and re-education of his faulty food habits are the true solutions to correction of obesity. (Ann. Int. Med., May '48 - M. M. Kunde)

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Immediate Fatalities After Intravenous Mercurial Diuretics: Sudden deaths shortly after the intravenous injection of various mercurial diuretics, although rare, have been reported with increasing frequency in recent years. Reported instances of fatalities within a few minutes after the injection, and apparently caused by it, now total 32. Deaths occurring many hours or days after the injection, even though there appears to be a definite relationship, are not included, since the mechanism is entirely different. In addition to the fatalities, there have been many very severe reactions recorded, and undoubtedly many more that were never reported. A study of the descriptions of these cases shows that in most instances it was merely by the greatest good fortune that they were not fatal, so closely do they resemble the fatal ones. There have been reports of several cases in which the intravenous injection of the mercurial diuretic may have been the direct cause of death, but in which the time relations, moribund condition of the patient, and other factors leave room for doubt about the role of the mercurial.

All of the 32 deaths occurred after intravenous injection. None has ever been recorded following administration by any other route. The fatalities were caused by many different drugs: Mercupurin, Salyrgan, Neptal, Esidrone, and Mersalyl. The majority followed the use of Mercupurin or Salyrgan, probably because they have been employed much more often than the others. Age and sex seemed to play no role. The diagnoses were: congestive heart failure, 16; nephritis, 7; nephrotic stage of nephritis, 4; nephrosis, 4; unknown, 1. From these diagnoses it does not appear that mercurial diuretics are more dangerous in one type of condition than in another, considering that the two commonest indications for their use are congestive heart failure and nephritis. The number of injections prior to the fatal one was most varied. Six deaths occurred with the first injection; eleven with the second, third or fourth; at the other extreme, some patients had 42 or 100 or even 200 previous injections. The interval between the preceding injection and the fatal injection is apparently of no significance; it was frequently from 1 to 4 days, but was occasionally several weeks

or months. The quantity given was usually 2 c.c. in adults and 1 c.c. in children. It must not be assumed that the patients were moribund when they received the last injection because many were ambulatory and apparently doing well.

Clinically, the fatal reaction usually starts from one to 3 minutes after completion of the intravenous injection. Frequently the patient cries out or gasps; cyanosis and pallor may be marked; substernal distress, dyspnea, orthopnea, irregular and labored respirations are common; convulsions are frequent; dilatation of the pupils is occasionally seen. There may be palpitation, tachycardia, fall in blood pressure, and irregularity of the cardiac rhythm; coma, cessation of respiration and of heart beat then occur. There have been numerous cases in which many of the above symptoms and signs were present and in which a fatal outcome seemed certain, but in which recovery occurred without specific therapy. Another group of cases is that in which symptoms, sometimes exceedingly severe or even fatal, are due to salt depletion and upset of the electrolyte balance caused by the marked diuresis. These symptoms usually start from 6 to 12 hours after the injection. Some minor or severe reactions are undoubtedly on an allergic basis. Finally, some cases, including a few fatal ones, are obviously due to mercury poisoning in the usual sense, affecting the alimentary tract or the kidneys.

The mechanism of sudden, immediate fatalities following the intravenous administration of mercurial diuretics has been clearly elucidated by several groups of investigators working with dogs and cats and by some clinicians in humans. Death is caused by a direct action of the mercury in these drugs on the cardiac musculature. An early manifestation is a change in intraventricular conduction, and the terminal effect is usually ventricular fibrillation. The evidence, experimental and clinical, of the toxic effect of mercury on the heart muscle seems definite and conclusive.

Based on recent studies by various investigators, some suggestions for trying to avoid sudden, immediate fatalities and near-fatalities are as follows:

1. Use the intramuscular route whenever satisfactory diuresis is thereby obtained. For this, Mercuhydrin appears to be the best drug, since it is effective and at the same time the least irritating. As pointed out previously, no death has been reported thus far by any route other than the intravenous. This is undoubtedly due in part to the fact that the intravenous is the most common method of administration; but on theoretical grounds this should be the most dangerous route because death is caused by the sudden action of the mercurial on the cardiac musculature.

2. Use the oral or rectal route for maintenance doses when sufficient diuresis is thus obtained without gastric or rectal irritation.

3. Use the intravenous route when the above methods do not suffice or when rapid and certain diuresis is imperative. One should employ the smallest

efficacious dose, rarely more than 1 c.c. Although the statement is frequently made that the size of the dose does not influence the fatality rate, it seems logical to give the smallest amount that produces a good therapeutic effect.

4. Give small amounts for the first three intravenous injections, since 6 of the 32 deaths occurred with the first injection and 8 more with the second or third. The first injection should not exceed 0.5 c.c. and the next two 1 c.c. unless the condition of the patient is desperate and the added risk of large initial amounts is justified.

5. Administer acidifying salts, such as ammonium chloride, from 6 to 12 Gm., daily, for at least 48 hours prior to each injection. Acidifying salts often induce diuresis, but not so satisfactorily or reliably as when followed by a mercurial. By combining the action of the acidifying compounds with that of the mercurials, less of the latter can be given and also satisfactory diuresis may be obtained by some route other than the intravenous.

6. Employ slow, intermittent injection, 0.1 c.c. every 15 seconds, either routinely or at least for the first three intravenous injections and in those patients exhibiting any reaction to previous injections. Although some authors state that slow injection does not reduce the incidence of these sudden deaths, any measure that might reduce the number of these unfortunate accidents is worthwhile.

7. Change to another mercurial diuretic in individuals exhibiting any sort of allergic reaction.

8. Administer mercurial diuretics only when clearly indicated, and when danger signals occur, complete re-evaluation of the therapeutic regimen is warranted. The warning reactions consist of any of the following: rash, urticaria, angioneurotic edema, chills, fever, pallor, cyanosis, substernal distress, palpitation, tachycardia, fall in blood pressure, cardiac arrhythmias, dyspnea, orthopnea, shock, collapse, and convulsions.

With respect to patients who have had a sudden, immediate and near-fatal reaction, the author believes that they should never again have intravenous injections of any mercurial, even though Ben-Asher had some patients who had no further reactions when given intermittent injections or sodium thiosulfate prior to injections. Most of his patients who had a severe, immediate reaction died from 6 to 10 weeks thereafter. He believes that the markedly diseased heart muscle is particularly sensitive to the mercurial diuretics. This seems a good reason for giving these patients no further intravenous injections of these compounds.

The suggestion of administering sodium thiosulfate intravenously prior to each intravenous injection of a mercurial seems impractical. However, the suggestion of incorporating a small quantity of magnesium sulfate or of ascorbic acid into mercurial diuretics for intravenous use, based on the experimental observation that the addition tends to prevent ventricular fibrillation or asystole

and death, seems logical, safe, and simple. If such a modified mercurial diuretic becomes available commercially, it would probably be safer than any now obtainable.

There is no evidence that death is more likely to occur when drugs such as ammonium chloride, phenobarbital, or digitalis are given with the mercurial diuretic; and a relatively good state of health is no protection against a fatal reaction. The recoveries in the immediate, near-fatal reactions appear to be spontaneous. There is at present no known specific treatment for the usual type of severe reaction. The doctor will try artificial respiration and epinephrine, but recovery will depend on the ability of the heart muscle to recover from the ventricular arrhythmia caused by the mercurial. (Ann. Int. Med., May '48 - R. E. Kaufman)

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The Thymol Turbidity Test in Various Diseases: The thymol turbidity test was first described by Maclagan in 1944 as an index of liver function. The exact mechanism of the test has not yet been completely determined. The turbidity is due to the formation of a complex consisting of a globulin, phospholipid, cholesterol, and thymol. Maclagan believed that the globulin was gamma globulin and that the thymol turbidity and cephalin flocculation tests had a similar mechanism. Recant and co-workers, using electrophoretic methods, were able to show that gamma globulin was not involved in the mechanism of the thymol turbidity test, whereas the cephalin flocculation test depended on the presence of gamma globulin. Recently Cohen and Thompson presented evidence that the protein in the complex of the positive thymol turbidity test was beta globulin. Clinically, investigators have felt that the basic mechanisms of the thymol turbidity test and the cephalin flocculation test were different. Kunkel and Hoagland have offered experimental evidence to show that the development of turbidity depends on both lipids and gamma globulins in the serum. However, the lipid protein complex migrates in the beta globulin fraction of the serum.

The thymol turbidity test has many advantages over other tests of liver function in current use, that is, stability of reagents, quantitative method of determination, short interval of time needed for performance, and apparent sensitivity. It was therefore decided to evaluate this procedure by testing sera from patients with liver disease as well as various other diseases.

The technic used for the performance of the thymol turbidity test by the author was the modification suggested by Shank and Hoagland. Sera showing 5 or more units were classed as abnormal. This was based on the author's observations of the test and on the investigations of Hoagland and Shank. These workers used 4.7 units as the upper limit of normal. A cephalin flocculation test was performed on each serum at the same time that the thymol turbidity determination was done. The cephalin flocculation test was read at the end of

48 hours and was called positive if it read 3 plus or 4 plus. In most instances total protein and formol gel determinations were also carried out. Bromsulfalein tests were done when indicated.

Although many of the patients tested were thought to have liver dysfunction, a large number of tests were made on patients in whom liver disease was not thought to be present. Many patients were tested repeatedly.

Tests were carried out one or more times on 567 persons. Seventy-four of these were regarded as normal controls. The results are presented in Table I, in which an attempt has been made to classify the cases.

TABLE I

GROUP	NUMBER OF CASES	NUMBER T.T.+	PER CENT T.T.+	POSITIVE THYMOL TURBIDITY TESTS	
				AVERAGE NUMBER OF UNITS	RANGE
Infectious hepatitis	36	34	94.5	23	5 - 50
Cirrhosis of the liver	48	46	96	20	5 - 49
Obstructive jaundice	12	5	42.5	17	6½- 38
Diseases of the gall bladder	11	6	54.5	8	5 - 20
Weil's disease	4	4	100	17.4	8 - 28½
Diseases with widespread liver destruction	11	8	73	14	6 - 33½
Neurosyphilis with fever therapy	9	9	100	19	8 - 28
Neurosyphilis without fever therapy	9	2	22.2	10.3	6½- 14
Acute lymphogranuloma venereum	21	20	95.3	13.6	5 - 35
Acute and chronic rheumatoid arthritis	17	14	82.4	10	5 - 19
Acute rheumatic fever	11	6	54.5	6.7	5 - 9
Congestive heart failure	56	27	48	8.4	5 - 25
Heart disease without failure	19	9	47	8.4	7 - 15½
Chronic lung disease	28	15	53.5	11	5 - 26
Acute infectious diseases	67	25	37.3	9	5 - 53
Neoplastic disease	15	7	46.5	9.5	5 - 16
Diabetes mellitus	19	6	31.6	8.6	5½- 10½
Ulcers and gastrointestinal hemorrhage	18	3	16.7	8	6½- 11½
Thyrotoxicosis	7	4	57	9.8	5½- 14
Nutritional disease	10	6	60	8	5 - 16½
Chronic ulcerative colitis	3	2	67	9	6 - 12
Amebiasis	4	0	-	-	-
Hemolytic crises	5	4	80	8	6 - 11½
Chronic alcoholism	4	0	-	-	-
Miscellaneous	49	28	57		
Controls	74	6	8	7.5	6½- 9½
Total	567	295	52		

Seventy-four members of the medical and nursing staffs were included in the group of controls. Six, or 8 percent, had positive thymol turbidity tests, ranging between 5.0 and 9.5 units. Most other workers have reported that the normal control subjects did not give values above from 4.0 to 4.7 thymol turbidity units. Ley and co-workers, however, determined their normal values for the thymol turbidity test statistically and concluded that the upper limit of normal was 8.7 units. Using this figure as the maximal normal level, 1.9 percent of their controls had an elevated thymol turbidity test. It is of interest to note that the thymol turbidity test in 8.5 percent of their controls exceeded 5 units.

Although there is both experimental and clinical evidence that the thymol turbidity and cephalin flocculation tests depend on different factors, it was of interest to compare the two tests in this series since both are generally

regarded as liver function tests. Table II shows the comparative results of the two tests in some of the larger groups of patients in the present series of cases.

TABLE II. COMPARISON OF THE THYMOL TURBIDITY AND CEPHALIN FLOCCULATION TESTS

GROUP	NUMBER OF CASES	T.T. + C.F. +	T.T. + C.F. –	T.T. – C.F. +	T.T. – C.F. –
Infectious hepatitis	36	27	7	1	1
Cirrhosis	48	37	9	1	1
Obstructive jaundice	12	2	3	1	6
Lymphogranuloma venereum	21	19	1	1	-
Neurosyphilis with fever therapy	9	9	-	-	-

Repeated examinations of the patients with infectious hepatitis with the two tests also indicated that the thymol turbidity was a better test for following the progress of infectious hepatitis than the cephalin flocculation, since it remained positive as long as there were any symptoms of the disease.

The results of the thymol turbidity and cephalin flocculation tests were in agreement in 69 percent of the cases in this study. The thymol turbidity was positive and the cephalin flocculation negative in 25 percent of the cases; the thymol turbidity was negative and the cephalin flocculation positive in 6 percent of the cases. Therefore, it would seem that the thymol turbidity test is considerably more sensitive than the cephalin flocculation test.

It appears from the results presented that the thymol turbidity test cannot be regarded solely as a test of liver function because positive results were frequently obtained in diseases in which there was no other evidence of liver dysfunction. The thymol turbidity test should be looked upon only as a measure of abnormal serum protein pattern, not necessarily related to liver function. It is conceivable that many conditions other than liver disease might occasion a change in the pattern of the serum proteins. Evidence in favor of this hypothesis is offered by the number of positive thymol turbidity tests in the control series of apparently normal healthy young men and women of the professional staffs.

The thymol turbidity test is a rather sensitive test in such diseases as infectious hepatitis, cirrhosis, Weil's disease, malaria, and so forth. Although it is a great aid in the diagnosis of these conditions, it can be used to follow the progress only of infectious hepatitis and probably Weil's disease. Labby and co-workers have shown that neither the thymol turbidity nor the cephalin flocculation test is of value in following the progress of cases of cirrhosis.

There are certain features of rheumatoid arthritis (palmar erythema, the remission of symptoms with the onset of jaundice, and the positive liver function studies) which seem to indicate dysfunction in the liver in rheumatoid arthritis. The high percentage of positive thymol turbidity tests in this disease adds another link in the circumstantial evidence of such a relationship.

It has long been recognized that lymphogranuloma venerum is a generalized disease. The incidence of this disease is rather high among some groups of

Negroes. Beeson and Miller have shown that many Negroes have abnormal serum protein reactions as evidenced by positive formol gel reactions. They postulated the possibility that these two findings were related. The high incidence of positive thymol turbidity and cephalin flocculation tests in lymphogranuloma venereum tends to confirm this hypothesis.

Negative thymol turbidity and cephalin flocculation tests are helpful in the differential diagnosis between obstructive jaundice and hepatogenous jaundice. Positive results, however, should not be relied upon to rule out the possibility of obstructive jaundice. The thymol turbidity test is frequently positive if obstruction is complicated by cholangitis. (J. Lab. and Clin. Med., May '48 - H. B. Stillerman)

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Further Studies on the Weltmann Serum Coagulation Reaction: Weltmann, in 1930, described a serum coagulation reaction which has shown itself to be of considerable clinical significance. He found that when normal human blood serum was diluted with distilled water 1:50 and boiled, the proteins failed to coagulate. However, when a small amount of electrolyte such as calcium chloride, magnesium chloride, or barium chloride was added, coagulation occurred. In certain pathologic conditions Weltmann noted that the serum required greater than normal concentrations of electrolyte in order for protein coagulation to occur, whereas in other conditions less than the normal concentration of electrolyte was required for coagulation. If 0.1 ml. of normal serum was added to 5 ml. of .04-percent calcium chloride solution and boiled, the protein coagulated. However, if the serum was added to .02-percent calcium chloride, coagulation did not take place.

Exudative and inflammatory processes so altered the blood serum that coagulation of the protein occurred only in concentrations of calcium chloride higher than .04 percent. Conversely, fibrosing processes so altered the serum that coagulation occurred in concentrations of calcium chloride lower than .04 percent. From these findings Weltmann devised the relatively simple test described subsequently.

Various theories were propounded to explain the mechanism of the Weltmann reaction. Alterations in the following factors, either singly or in combination, were suggested as the basis of the reaction: the pH of the calcium chloride solutions employed, the pH of the serum, the serum calcium concentration, the total blood globulin, the albumin-globulin ratio, and the blood fibrinogen. Dees studied the reaction extensively and suggested that the serum lipids are an important factor in the coagulation reaction. However, Scherlis and Levy showed that the coagulation reaction is closely related to changes in the percentage of alpha globulin in the blood.

There follows a description of the technic of the Weltmann test:

Ten test tubes are set up in a rack and are numbered from 1 to 10 from left to right. From a stock solution of .1-percent calcium chloride ($CaCl_2 6H_2O$) measured amounts are pipetted into each tube starting with 5 ml. in the first tube and decreasing by 0.5 ml. in each tube so that tube 10 contains .5 milliliter. Sufficient distilled water is added so that each tube will contain a total of 5 ml. of solution, that is 4.5 ml. of water are added to tube 10, 4 ml. to tube 9, and so on in decreasing amounts to .5 ml. in tube 2. This procedure results in 10 dilutions of calcium chloride ranging from .1 percent in tube 1 down to .01 percent in tube 10.

To each tube is then added 0.1 ml. of the blood serum to be tested. The serum must not contain hemolyzed blood. After shaking, the tubes in their rack are placed in a boiling water bath for exactly 15 minutes. The rack of tubes is then removed from the bath and the number of tubes in which coagulation has occurred is recorded. The coagulum appears as a flocculation. Coagulation normally appears in the tubes of higher concentration (Tubes from 1 to 6) and not in the tubes of lower concentration (Tubes from 7 to 10). The number of the tube containing the most dilute solution of calcium chloride in which coagulation has occurred gives the reading for the test. Thus, if coagulation occurs in tubes from 1 through 6, the coagulation band is 6 (C. B. 6 or Weltmann 6). Care must be taken to determine the last tube in which actual coagulation has occurred, since clouding or turbidity may occur in two or three tubes more dilute than the significant tube. With normal human serum, coagulation usually occurs in the first 5, 6, or 7 tubes (C. B. 5 or 6 or 7). When the coagulation band is less than 5, it is said to shift to the left, and when it is more than 7, it is said to shift to the right.

In actual practice this technic has been simplified by the authors to ease the burden on the technician without sacrificing accuracy. If coagulation occurs in any tube, by definition, it will also occur in every tube to the left of it (that is, in all higher concentrations). Therefore, tubes 1, 2, 9, and 10 are not routinely set up, since coagulation usually occurs in at least three tubes and rarely occurs in more than eight tubes. If, after the initial test is performed, no coagulation has occurred in tube 3, tubes 1 and 2 are set up separately and the serum sample is tested in these tubes. Conversely, if in the initial test coagulation has occurred in tube 8, tubes 9 and 10 are set up separately and the serum is tested in these tubes. For a single test this modification may seem of little value. However, when an average of five samples of serum are tested simultaneously in parallel rows of tubes, as is done in the authors' laboratory, the time and effort saved with this modification are considerable.

Weltmann demonstrated that in the presence of an exudative or inflammatory lesion there was a shift to the left of the coagulation band and that in the presence of fibrotic lesions there was a shift to the right. Subsequent investigators have corroborated these findings. However, the bulk of significant results appears

to be confined to the cases in which a shift to the left was obtained. This is in agreement with the findings of the authors.

Previous writers have found the coagulation band of normal sera to be rather fixed at 6 or 7. The authors, however, found that they had to consider the normal range as varying from 5 to 7. Wachstein also designated a coagulation band of less than 5 as being significantly shortened, regarding a coagulation band of 5 as being "suggestively shortened."

In a report by Kraemer, one of the authors, in 1942, his results with the Weltmann reaction as performed on about 1,100 patients were summarized. The present report includes that material plus the results obtained with sera from about 1,870 additional patients, a total of 3,954 Weltmann tests having been performed on about 3,000 consecutive private patients.

During the period covered in this report, a Weltmann coagulation test as well as a complete blood count, urinalysis, and sedimentation rate (Westergren or Cutler) was performed at least once on each patient in addition to other indicated diagnostic procedures. Most of the patients presented gastro-intestinal problems, and it is in this group that the authors have been able to follow the results of the Weltmann reaction with the greatest degree of accuracy.

Of the 3,954 Weltmann tests performed, a total of 281 showed a coagulation band of 4 or less. It was possible to correlate closely the clinical or pathologic findings with the low Weltmann reactions in 237 of these cases. In the remaining 44 cases no such correlation was possible.

In 55.6 percent of cases of regional ileitis the Weltmann was 4 or less, this being the highest percentage in this series. In 50 percent of cases of diverticulitis coli and in 41.4 percent of cases of proved gastric carcinoma, the Weltmann was 4 or less. In cases of ulcerative colitis, gastric ulcer, cholecystitis, and choledocholithiasis also significantly high percentages of low Weltmanns, 35.2, 32 and 30 percent respectively were shown. Conversely, in cases of duodenal ulcer, cholecystitis, and cholelithiasis the lowest percentages of low Weltmanns were shown, although it has been the authors' experience that in cases of penetrating duodenal ulcer and in ulcer with obstruction the incidence of low Weltmann reactions has been relatively high. These results appear to confirm the finding that the coagulation band is shortened in the presence of exudative or inflammatory lesions. Ulcerative colitis is characterized by marked exudative and ulcerative inflammation. Gastric ulcer, penetrating duodenal ulcer, and obstructive duodenal ulcers are generally associated with considerable inflammatory reactions, and choledocholithiasis is in many instances the cause of chronic low-grade inflammation in the biliary tree. With regard to ulcerative colitis the view that an incidence of 35.2 percent positive Weltmanns is relatively low might be taken, considering the characteristic pathology of the disease. It should be mentioned, therefore, that a number of the cases studied were quiescent at the time of study and have remained so.

Gastro-intestinal cancer, especially gastric cancer, is often associated with secondary ulceration and inflammation, and the latter is probably responsible for the low Weltmann rather than the malignancy per se. The authors have observed a number of cases which would seem to substantiate this fact.

The Weltmann serum coagulation reaction appears to be of sufficient value as a laboratory diagnostic aid to warrant its routine use in gastro-enterological diagnosis. Admittedly it is a nonspecific reaction, but this fact does not detract from its utility. In the presence of exudative or chronic inflammatory reaction the Weltmann coagulation band is shifted to the left in a significant number of instances. It has been the authors' experience and that of others that, in general, whenever there is a low Weltmann the sedimentation rate is elevated, but there is no correlation between these findings. With a Weltmann of 4 a low or high sedimentation rate may be found, whereas the same sedimentation rate may be noted with a Weltmann of 6 or 2. The sedimentation rate is often influenced by a number of factors, many of them of relatively minor nature, and it thereby loses diagnostic significance. The Weltmann reaction, however, when positive, that is when 4 or less, usually indicates, in gastro-intestinal complaints, an inflammatory lesion of serious import and rapidly reverts to normal when this lesion is healed or removed. It is on this account helpful in both diagnosis and prognosis.

The 44 patients with positive Weltmanns in whom the cause of the positive reaction was not determined almost without exception consisted of those who were seen only once; therefore an adequate diagnostic work-up and follow-up were not possible. More thorough study probably would have revealed the pathologic basis for the positive test in all or most of these patients, but the possibility of false positive reactions in this group cannot be ruled out. However, in the 237 patients in whom adequate study was performed, a small number of positive tests was obtained in inflammatory states such as acute severe gingivitis, acute tonsillitis, or acute sinusitis; with subsidence of the inflammation the Weltmann reaction in these instances rapidly reverted to normal. The incidence of actual false positive reactions, that is positive reaction in the absence of any demonstrable inflammatory or exudative lesion, must be very slight.

It would be unwise to attribute to the Weltmann reaction values which it does not have. Many cases of serious disease of the gastro-intestinal tract have been diagnosed in the presence of a normal Weltmann. However, when the Weltmann has been positive, complete diagnostic work-up has usually revealed a lesion of importance. This has led the authors to the clinical assumption that a patient with a low Weltmann reaction has a serious illness until absolutely proved otherwise. In a number of instances the cause of a low Weltmann has been traced to important lesions outside the gastro-intestinal tract after gastro-intestinal work-up had revealed a lesion sufficient to explain the presenting symptoms but not sufficient to explain the low Weltmann reactions. (J. Lab. and Clin. Med., May '48 - L. H. Siegel and M. Kraemer)

Partial Resistance of a Strain of Bedbugs to DDT Residual: In the summer of 1947 several instances, chiefly in the barracks of the Naval Receiving Station, Pearl Harbor, were noted of the failure of DDT residual spraying to control an infestation of bedbugs (Cimex lectularius). Since DDT had become available in the Fourteenth Naval District in the latter part of 1944, it had been remarkably effective in bedbug control. Any barracks or other building in which mattresses and bunks were sprayed with DDT/kerosene solution had promptly become free of bedbugs, and had remained free for more than six months. The complete and prolonged control of bedbug infestation following DDT residual spraying was consistent with experience reported elsewhere.

When the first instances were noted, in June and July of 1947, of persisting bedbug infestation following DDT spraying, it was at first supposed that the failure to control the bedbug infestation was due to incomplete or inadequate spraying. It soon became apparent, however, that this explanation was not a sufficient one, for bedbugs were found alive and uninjured inside bedspring coils whitened with DDT residue from previous spraying with emulsion. Although more dead bedbugs were seen than live ones, persistent or recurrent infestation seemed to indicate that the bedbug population, or part of the population, was less than normally susceptible to DDT for ordinarily death would be expected to occur within 24 hours following exposure for 15 minutes to DDT residual.

Tests were undertaken to determine conditions and extent of the resistance of these bedbugs to DDT residual.

For testing the effect of DDT residual, pieces of paper towel, approximately 1.5 x 2.5 inches, were saturated with 5-percent DDT/kerosene solution and afterwards thoroughly dried, and others dusted with 10-percent DDT powder. These patches of paper were placed singly in test tubes. Specimens of the apparently resistant bedbugs exposed in these tubes were alive and apparently unaffected after 24 hours or more whereas various other insects including cockroaches, similarly tested, were killed, or they manifested incoordination usually within from 6 to 10 hours. Although these bedbugs appeared unaffected after exposure for 24 hours, they were killed after prolonged exposure. The time to death of two bedbugs exposed to residual of 10-percent DDT powder was 6 days; 6 days was also the minimum time to death of bedbugs exposed to dried residual of 5-percent DDT/kerosene solution, when bedbugs spent half their time or more in contact with the treated surface. Their survival for two weeks or more while exposed to DDT residual was not unusual.

The contact time of insects on treated paper varies with the position of the paper in the test tube, and whether the test tube is horizontal or upright. When treated paper is curved against the side of the test tube so that the bedbug can cross it or leave it, there can be no control of the time of exposure. An attempt was made to remove this variable by cutting paper towel, soaked in DDT/kerosene and then dried, into 1/4-inch squares. When 3 such squares

are placed in the bottom of a test tube, and the test tube supported in an upright position, a bedbug placed in the test tube remains continuously in close contact with the treated paper. Continuous contact with the small area of treated paper in this test apparently was no more toxic than intermittent exposure to a larger area in the previous test. Two adult bedbugs exposed to this continuous contact with DDT residual survived more than three weeks. Nymphs probably are somewhat less resistant to DDT residual than are the adults, though too few instances have been observed to confirm the point.

A bedbug exposed to a piece of paper towel freshly wet with DDT/kerosene solution was alive and apparently unaffected after 24 hours, but dead before the third day.

One of the earliest indications of the effect of DDT on bedbugs is their refusal to eat. Ordinarily, one of these DDT-resistant bedbugs, exposed to DDT residual, dies within a day or two of the time it refuses to feed (if it has been a week or more without feeding) or shows any evidence of trembling incoordination. Two adult bedbugs, after 8 days of continuous contact with DDT-impregnated paper, ate readily (engorged with blood) and appeared normal in behavior otherwise. One of these adult bedbugs was fed again and ate readily six days later upon completion of two weeks in contact with DDT residual. These adult bedbugs laid eggs which were secured to the DDT-impregnated paper. Some of the eggs hatched. Three nymphs of undetermined age, but only a few days old, which were in continuous contact with DDT-impregnated paper fed readily, engorging themselves with blood. One lived 2 days, one 3 days, and the other was alive and alert at the end of 6 days after feeding. The fed nymphs were readily distinguishable from the unfed nymphs hatching afterwards. Of 7 other nymphs hatched later and fed, 6 were alive at the end of 12 days of continuous exposure to DDT residual-treated paper.

The DDT-resistant strain of bedbugs, presumably genetically distinct in possessing the character of DDT tolerance, responsible for occasional minor outbreaks of infestation in barracks of Naval Receiving Station, Pearl Harbor, is by no means completely resistant to, or unaffected by, the residual DDT. The life expectancy of bedbugs exposed to DDT residual is markedly shortened. However, the degree of DDT resistance is such that, in the case of these bedbugs, DDT residual spraying can no longer be counted an effective and dependable means of control. Fortunately, the bedbugs are susceptible to the oily solvent of DDT/kerosene spray, and attempts are made to kill as many of the insects as possible by contact with the spray solution, minimizing the dependence on residual effect for control. A much heavier rate of application of the spray is made than was formerly necessary for control of a bedbug population normally susceptible to the killing action of DDT residual.

Inspections are made and reports of the occurrence of bedbugs are invited to insure that any infestation of bedbugs that occurs can be dealt with while it is still minor. No infestations have so far been noted that cannot be dealt with effectively on this basis.

It is suggested that Medical Department personnel in other areas and on board ships be on the alert to detect and control bedbug infestations that may occur, especially infestations not readily controllable by DDT residual spraying. (M. S. Johnson, Lieut. Comdr., MSC, USNR and A. J. Hill, HMC, USN)

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Flies and Poliomyelitis: Efforts to abate poliomyelitis epidemics by intensive fly control have given little promise of success or of proving or disproving the proposition that flies are an important means of transmitting poliomyelitis. For the present, it does not appear justifiable for the Public Health Service or other public health agencies to engage in emergency fly control activities during epidemics of poliomyelitis to learn more about the role of flies in the dissemination of this disease. More exact scientific investigations on this point are necessary.

Although the Public Health Service does not discourage fly control when such activity can be carried out on a continuing and rational basis, the spectacular work by airplane and ground machines that has been carried on during emergencies may give an unjustified feeling of security and divert attention from other possible sources of poliomyelitis spread.

As a result of experimental work, the following facts are known concerning transmission of poliomyelitis by flies:

a. Poliomyelitis virus can be found for considerable periods of time in the stools of infected persons and in sewage containing such stools.

b. Poliomyelitis virus has been isolated repeatedly from flies (houseflies and blow-flies) during epidemics.

c. The infection of experimental animals by the ingestion of materials containing poliomyelitis virus has been demonstrated on numerous occasions.

d. It has been shown once, although not yet confirmed, that flies in the home of a person with poliomyelitis became contaminated naturally with poliomyelitis virus and conveyed enough of it to food, which had no other contact with virus, so that poliomyelitis-free chimpanzees developed infections of poliomyelitis shortly after eating contaminated food.

The above indicates that flies can transmit poliomyelitis. It does not show how frequently this happens, it does not exclude other means of transmission; nor does it indicate how important fly transmission is in comparison with other means of transmission. (The Communicable Disease Center of the U. S. Public Health Service, Atlanta, Georgia, recently released the above to their representatives in the field.)

Studies in Experimental Dental Caries: From a statistical analysis of data observed in recent studies involving the relationships of diet to dental caries in experimental animals, it appeared that a sugar diet was less effective in producing caries than the regular laboratory chow, that a coarse corn diet was the most effective of the three, and that over the range existing in this particular study caries incidence varied inversely with water consumption. Further experiments are planned to explore for validity and expand these analytical indications for validity and expand them. (U.S. Naval Medical Research Institute, Bethesda, Md. - C. A. Schlack et al.)

* * * * * *

Dentistry - Control of the Gagging Patient: One of the most difficult problems the prosthodontist encounters is the gagging patient. Some of the patients with a gagging tendency are nervous and apprehensive but can be controlled by explaining to them what is to be done in the process of taking an impression and by developing in them through the dentist's manner and approach the assurance that every degree of care and patience will be exercised.

An additional measure required for some patients is the use of topical anesthetic lozenges, such as Lozenge of Phenol or Troches of Elm - U. S. Dispensatory 23rd. Ed. - which will usually prove helpful. The lozenge should be dissolved in the mouth about 15 minutes before the impression is to be taken.

For some patients, these measures do not suffice, and in them the barbiturates or their compounds properly and carefully used will overcome the gagging tendency. Nembutal C acts quickly and effectively. Depending entirely upon the difficulty of the gagging patient, a dose of from 1/2 to 2 gr. may be given. This should be administered from 30 to 45 minutes before impressions are to be started, preferably on an empty stomach. Usually it is best to allow the patient to remain in the office for a while after the operation to permit the effects of the drug to subside.

A teaspoon with a round end may be used to remove any material from the distal border of the impression that interferes with the comfort of the patient.

(Two useful procedures, not involving the use of drugs, are (1) instructing the patient to breath through the mouth, and (2) having the patient incline the head forward, to allay the fear or sensation of impression compound passing into the throat.) (Texas State Dent. J., Oct. '47 - O. M. Dresen)

* * * * * *

New and Broader Phase of the Navy's Medical Training Program: The Surgeon General of the U. S. Navy has announced the expansion of the professional training program for medical officers of the Reserve and regular Navy; this is similar to the recently expanded Army medical training program. The object is to permit more Navy doctors to meet the requirements for certification by the various American Specialty boards, and to encourage the young doctor to intern under the auspices of the Navy. The following are the important points in this program:

Graduates of medical schools approved by the Council on Medical Education and Hospitals of the American Medical Association who have been accepted for internship by a hospital approved for such training may be commissioned as lieutenants (junior grade), MC, USNR, and permitted to carry out their civilian intern training. They will receive all the pay and allowance of the rank while so serving. After completing their internships, the medical officers must remain on active duty for a period of one year. If they meet the requirements, they will be given every encouragement to transfer to the regular Navy.

Doctors who complete the one year of obligated Naval service following their civilian internship, and who transfer to the regular Navy, become eligible for residency training on a competitive basis with other medical officers of the regular Navy.

Resident physicians and physicians accepted for residencies, in civilian hospitals approved for residency training, are eligible for commission in the regular Navy. Those so commissioned will be assigned to duty (with full pay and allowances) in the hospital in which they are already a resident, or in which they have been accepted for residency training. Every attempt will be made to permit such residents holding commissions in the regular Navy to complete their training in event of an emergency.

The Navy has at the present time 400 approved residencies and fellowships, in the various specialties recognized by the American Specialty Boards, in Naval and civilian hospitals and institutions. This educational training involving the 400 residencies is divided into 2 programs.

Program A: One hundred of these residencies, courses, and fellowships will be made available for civilian physicians accepting a commission in the U. S. Navy. An additional 100 civilian physicians will be commissioned in the U. S. Navy and permitted to pursue their own course, fellowship, or residency, provided it is approved by the Council on Medical Education and Hospitals of the American Medical Association with concurrence of the Specialty Board. Upon acceptance of the designated training, they will be required to agree to remain in the Navy for a certain obligated time.

If on original appointment a candidate has not been approved for more than one year of training, during his first year of residency training (Program A), he

may compete for one of the 300 residencies (Program B) available to the medical officers of the regular Navy, and if he obtains such training, he will obligate himself to remain on active duty for an additional period depending upon the amount of time spent in training.

Program B: Three hundred residencies, fellowships, or courses will be reserved for continuing the Training Program as presently organized for medical officers of the regular Navy.

The obligated service following graduate medical training (courses, fellowships and residencies) in Naval hospitals is one year for each year of training received.

Information concerning any part of the program may be obtained by writing to the Chief of the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

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Physical Examinations for Appointment or Promotion in USN and USNR: The BuPers circular letter noted on page 40 of this issue contains important information for those (1) concerned with the appointment of the boards of medical examiners, or medical examiners, (2) those serving as medical examiners, and (3) those connected with the paper work incident to the appointment and functioning of the boards.

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Portable Resuscitator of Intermittent Positive Pressure Type Now Available: Stock No. 3-599-940, Resuscitator, Portable, Intermittent Positive Pressure is hereby removed from the Addenda to the Army-Navy Catalog of Medical Materiel and made available for issue. Suggest one (1) for Shore Stations; Ships - in accordance with current ship's allowance list. Attention is invited to the fact that this item should not be requisitioned if old type resuscitators are on hand and considered adequate. (Materiel Div., BuMed)

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BUMED CIRCULAR LETTER 48-61 27 May 1948

To: All Ships and Stations

Subj: Civilian Medical, Dental, and Hospital Treatment of Naval Personnel

Refs: (a) Article 1189(1), N.R.
(b) Paragraph 315, Manual Medical Department

1. Public Law 511 - 80th Congress, which was approved on 4 May 1948, is quoted below for the information of all concerned:

> "To authorize the payment of certain claims for medical treatment of persons in the naval service; to repeal section 1586 of the Revised Statutes; and for other purposes.
>
> "Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That section 1586 of the Revised Statutes (U.S.C. Annotated, 1940 edition, title 34, sec. 921) is hereby repealed.
>
> "Sec. 2. The Secretary of the Navy is authorized and directed to promulgate regulations providing for the reimbursement of persons in the naval service for the cost of emergency or necessary medical services, including hospital service and medicines, from civilian sources when the person receiving the service is in a duty status: Provided, however, That reimbursement will be made under this Act only if it is determined that no medical service was available from a Federal source.
>
> "Sec. 3. For the purpose of this Act a person shall be regarded as in a duty status in the naval service while on authorized liberty or leave.
>
> Approved May 4, 1948."

2. The prohibition contained in references (a) and (b) is accordingly null and void; and necessary civilian medical, dental, and hospital treatment may now be furnished naval officers in the same manner and to the same extent as is furnished enlisted Navy personnel. Regulations are now in the process of being revised and will be released to the naval service in the near future.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-62 - This letter is Restricted. It is of limited distribution and does not appear in the Navy Department Bulletin.

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BUMED CIRCULAR LETTER 48-63 2 June 1948

To: Medical Officers in Command, U. S. Naval Hospitals

Subj: Training Program for Members of Nurse Corps, U. S. Naval Reserve, on Active Duty for a Two Weeks' Training Period

This letter contains an outline of a training program that is to be followed for members (newly appointed and, as well, those with former service) of the Nurse Corps, U. S. Naval Reserve, who are on active duty for a training period of two weeks.

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BUMED CIRCULAR LETTER 48-64 3 June 1948

To: MedOfCom, U. S. Naval Hospitals; U. S. Naval Medical Supply Depots; National Naval Medical Center, Bethesda, Maryland; Naval Medical Center, Guam, Marianas Islands

Subj: Civilian Personnel Officer, Request for Information in Regard to

Ref: (a) Part 1, Chapter 5, Paragraph 1512, Manual of Medical Department, U. S. Navy

This letter requests addressees to forward to the Bureau the name, military rank, or civilian grade, as the case may be, of full-time civilian personnel officers of activities under their command and to keep the Bureau currently informed of any changes in such assignments that may occur.

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BUMED CIRCULAR LETTER 48-65 3 June 1948

To: Distribution List

Subj: Naval Medical Supply Depot, Oakland, California; Mission of

Ref: (a) CNO ltr Op-40U-aw, NT4-8/A3-1, Serial 383P40, dtd 21 May 1948 to BuMed.

1. In accordance with the authority contained in reference (a), the mission of the Naval Medical Supply Depot, Oakland, California, is as follows:

(a) To procure, store, prepare for shipment and deliver to transshipment agencies standard medical supplies and equipment for all U. S. Naval and Marine Corps activities and forces of the 11th, 12th, and 13th Naval Districts continentally, and for all overseas activities in the Pacific, including Northern and Western Pacific Ocean Areas. Such Medical supply support to be either directly or indirectly through ComSerPac and/or intermediary continental or extra-continental supply activities, as directed by cognizant authorities.

(b) To procure, store, prepare for shipment, and deliver to transshipment agencies standard medical supplies and equipment for: (1) all West Coast Fleet units, active and reserve, and assigned craft; and (2) to overseas units of the Pacific Fleet, such support to be either directly or indirectly through ComSerPac and/or intermediary continental or overseas supply activities, as directed by cognizant authorities.

(c) To maintain on hand, in accordance with CNO approval, such reserves of standard medical materials in stock as may be directed by the Bureau of Medicine and Surgery.

(d) To maintain technical control over all medical stores carried in stock at NSD, Clearfield, Utah, and at NSD, Spokane, Washington.

(e) To provide facilities for, and accomplish the salvage and repair of medical supplies and equipment.

(f) To maintain facilities for, and accomplish the assembly of such Medical Advance Base Components and Field Medical Units as may be directed by the Bureau of Medicine and Surgery.

(g) To identify and dispose of Navy surplus medical materials under the technical control of the Naval Medical Supply Depot.

(h) To perform such stores and cost accounting functions as may be directed by the Bureau of Medicine and Surgery.

(i) To perform additional accounting, incident to proper function of the depot, as may be designated by ComTwelve or other competent authorities, with the concurrence of the Chief of the Bureau of Medicine and Surgery.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-66 8 June 1948

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-5, MMD

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change 3-5 is effective immediately. It shall be recorded on the "Record of Changes" page in the Manual. The individual paragraph changes are to be inserted in their proper places in the Manual text. At a later date, these changes will be incorporated in printed page change 3.

--BuMed. C. A. Swanson

Note: The enclosure consists of six pages of miscellaneous changes.

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BUMED CIRCULAR LETTER 48-67 9 June 1948

To: Distribution List

Subj: Naval Medical Supply Depot, Brooklyn, N. Y.; Mission of

1. The mission of the Naval Medical Supply Depot, Brooklyn, N. Y. and of the Naval Medical Supply Depot Annex, Edgewater, N. J., is as follows:

(a) To receive, store, and distribute standard medical supplies and equipment for all U. S. Naval and Marine Corps activities and forces of all continental Naval Districts, except the 11th, 12th, and 13th; and for all overseas activities in the Atlantic Ocean and European areas.

(b) To receive, store, and distribute standard medical supplies and equipment for: (1) all East Coast fleet units, active and reserve, and assigned craft; and (2) all overseas units of the Atlantic Fleet, such support to be either directly or indirectly through ComSerLant and/or intermediary continental or overseas activities, as directed by cognizant authorities.

(c) To receive, store, and distribute standard medical supplies and equipment for U. S. or foreign government agencies as directed by CNO and BuMed.

(d) To maintain on hand, in accordance with CNO approval, such reserves of standard medical materials in stock as may be directed by BuMed.

(e) To maintain technical control over all medical stores carried in stock at NSD, Mechanicsburg, Pa.

(f) To provide facilities for and accomplish the salvage and repair of medical supplies and equipment.

(g) To maintain facilities for and accomplish the assembly of such medical advance base components and field medical units as may be directed by BuMed.

(h) To identify and dispose of Navy surplus medical materials under the technical control of the Naval Medical Supply Depot.

(i) To organize and instruct the Naval Optical Repair Units.

(j) To indoctrinate and instruct personnel in the operation and maintenance of units in the echelons of Naval Medical Supply.

(k) To perform such stores and cost accounting functions as may be designated by BuMed.

(l) To perform additional accounting incident to proper function of the depot, the Naval Medical Material Office, and the Army-Navy Medical Procurement Office, as may be designated by ComThree or other competent authorities, with the concurrence of the Chief of the Bureau of Medicine and Surgery.

Approved: I. N. Kiland --BuMed. C. A. Swanson
Acting Deputy
Chief of Naval Operations (Logistics)

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BUMED CIRCULAR LETTER 48-68 10 June 1948

To: MOinC, All Naval Hospitals; SMO, USS Consolation, USS Repose; MOinC, Naval Medical School, Naval Medical Research Institute; Officer in Charge, Naval School of Hospital Administration

Subj: Diagnostic Nomenclature and List of Surgical Operations; Revision of

Encl: A. Tentative Revision of Diagnostic Nomenclature
B. Tentative Revision of List of Surgical Operations

1. The Secretary of National Defense has recognized the need for standardization in the field of diagnostic and related terms and has directed the production of a joint diagnostic nomenclature for use by all of the Armed Services. Enclosures A and B present tentative lists of terms proposed for inclusion in the joint nomenclature and list of operations. It is desired that the various fields covered by these lists be reviewed by appropriate members of your staffs and that comments and suggestions resulting from the review be assembled and forwarded to the Bureau. In view of the urgency expressed in the Secretary's directive, it is

desired that your comments and recommendations be forwarded as early as practicable, and prior to 15 July 1948.

2. Enclosure A is the result of joint efforts of the several armed services to arrive at a common list of diagnostic titles, and was undertaken with several objectives in view. The first of these was the inclusion only of acceptable medical terminology using as a guide the Standard Nomenclature of Disease of the American Medical Association. Occasional departures from this standard have seemed advisable both because of the peculiarities of naval and military medical practice, and because the Navy list of diseases is not only a nomenclature - i.e., a dictionary of acceptable diagnostic terms, but serves also as a statistical classification of morbid conditions. The departures from the Standard Nomenclature have been held to minimum, and conformance with its general aims has been preserved.

3. The second aim in the revision stems directly from the latter consideration above. It is to achieve a list that will fall readily into the rubrics of the new International Statistical Classification of Diseases, Injuries, and Causes of Death. This classification was recently adopted for world-wide use at the Sixth Conference for the revision of the International List of Causes of Death, in Paris, and represents the first attempt on an international scale to achieve uniformity in morbidity reporting in addition to reporting of deaths. Its adoption by the Armed Forces for their tabulations will permit wide comparability with other population groups.

4. The third objective sought in the present revision was the inclusion of titles representing the majority of conditions that will be encountered in naval and military practice, covering both active duty and supernumerary patients. The present "xy" categories will remain, and their use for conditions not included in the list is expected.

5. It should be pointed out that the particular order in which the diagnostic titles are listed in this draft is without significance except as an aid for reference purposes. The diagnoses are grouped under classes that have the same numbers as the present Navy nomenclature to facilitate review by Navy personnel. Classes XV and XXVII, covering mental and dental conditions are not included in this draft but will be circulated separately. No titles are listed under class XIV, Diseases of Lymphatic System, since Hodgkins Disease is shown with malignant neoplasms, and Lymphangitis, etc., are shown in class XIX, Diseases of Skin and Cellular Tissue. Class XXI, Miscellaneous Diseases and Conditions, has been reduced to cover only special admissions and no disease. Class XXIV, Female Diseases and Conditions, has been considerably expanded; comments from the Dependents' Services are particularly desired on this class as well as on the new classes XXXI and XXXII, Conditions of Early Infancy, and Congenital Malformations. Class XXVIII, Prophylactic Reactions and Therapeutic Misadventures, is a new class which is intended as an aid in locating cases of therapeutic accidents for study. Class XXXIII covers late effects of disease or injury, and includes titles previously carried in other classes.

6. The list of surgical operations is presented in Enclosure B in classified order, arranged in the form proposed for the final draft. With respect to the operation titles comments are desired not only upon the titles themselves, but upon the method of arranging the titles primarily by surgical specialties.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-69 11 June 1948

To: All Stations

Subj: Uniform Charge for Interdepartmental Hospitalization, Fiscal Year 1949

Ref: (a) Director, Bureau of the Budget, Exec. Office of the President ltr., to SecNav, dated 8 September 1947.
(b) Part IV, Chapter 1, ManMedDept, USN, 1945 Edition.
(c) Executive Order 9411, dated 23 December 1943.

This letter gives the rate, the disposition of net earned funds received locally and the accounting procedures to be followed in instances of the hospitalization of (1) interdepartmental personnel, (2) supernumaries within and outside the continental limits of the U. S., and (3) dependents of Navy and Marine Corps personnel. This letter in full is contained in the Navy Department Bulletin of 15 June 1948.

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BUMED CIRCULAR LETTER 48-70 17 June 1948

To: Commandants of Naval Districts; River Commands; Fleet Force, and Area Commanders

Subj: Medical and Dental Technical Equipment Maintenance Program, BuMed

This letter states (1) that the Bureau of Medicine and Surgery is instituting a program of Medical and Dental Technical Maintenance for equipment in naval medical and dental installations, (2) that at the present time, Medical and Dental Technical Repair Men are assigned in certain naval districts and vessels of the fleet, in addition to those attached to all naval medical supply depots, (3) that it is the intention of the Bureau to assign additional Technical Repair Men as they become available under the cognizance of the commandants of all remaining naval districts, river commands, and to ComSerPac and ComSerLant, (4) that due to the limited number of men trained in medical and dental technical repair service, it is imperative that their services be made available to activities and

vessels geographically adjacent to their respective locations, and (5) that full cooperation by cognizant authorities in providing shop space and transportation, including travel orders where indicated, is desired and necessary in order to insure the success of this program. Information is given concerning necessary tools, spare parts, accounting procedures, and reports.

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BUMED CIRCULAR LETTER 48-71 18 June 1948

To: MedOfCom, U.S. Naval Hospitals; U.S. Naval Medical Supply Depots; National Naval Medical Center, Bethesda, Maryland; Naval Medical Center, Guam, M. I.

Subj: Service Record Card for Civilian Employees

Refs: (a) Office of Industrial Relations, Navy Department ltr OIR:275:GLJ (CPL&D-48-51 DF) of 29 April 1948.
(b) Federal Personnel Manual, Pages R1-45 to R1-51.

This letter states (1) that reference (b) prescribes the use of standard form 7, Service Record Card, in personnel offices throughout the Federal Government, (2) that reference (a) provides instructions for ordering standard form 7, (3) that addressees should not enter into negotiations for the procurement of personnel forms from private concerns or have local personnel forms duplicated without prior approval of the Bureau, and (4) that each activity should insure that copies of Civilian Personnel Letters and Dispatches and Navy Civilian Personnel Instructions are routed immediately to the individual responsible, upon receipt, for their administration.

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BUMED CIRCULAR LETTER 48-72 22 June 1948

To: MOinC, Naval Hospitals

Subj: Naval Medical History

Encl: (A) HW - Suggested Activities of the Historical Officer at Naval Hospitals

This letter (1) directs addressees to designate a suitable officer for additional duty as Historical Officer, (2) includes a list of suggested activities for the Historical Officer, and (3) contains certain other instructions concerning the collection of data and the preservation of material of Naval medical historical importance.

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BUPERS CIRCULAR LETTER 48-95 14 May 1948

To: All Ships and Stations

Subj: Directives Governing Appointment of Boards of Medical Examiners

Refs: (a) BuPers Circ. Ltr. 248-47; N. D. Bul. of 31 Dec. 1947, 47-1198.
(b) JAG ltr. 48-256 (N. D. Bul. of 15 Apr. 1948).

Encl: (A) Summary of directives governing appointment of boards of medical examiners (or other medical examiners) for physical examinations for appointment or promotion in the Regular Navy and the Naval Reserve.

This letter is accompanied by the enclosure as above for the information and guidance of all commands authorized to appoint boards of medical examiners and for the guidance of the members serving on such boards. A copy of this enclosure (5 pages in length) is contained in the 31 May 1948 issue of the Navy Department Bulletin under Circular Letter 48-389, page 20.

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